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Health and Environmental Effects Profile for Propazine

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR PROPAZINE

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16. ABSTRACT

The Health and Environmental Effects Profile for propazine was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Propazine has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for propazine is 7.8×10^{-2} $(mg/kg\ bw/day)^{-1}$ for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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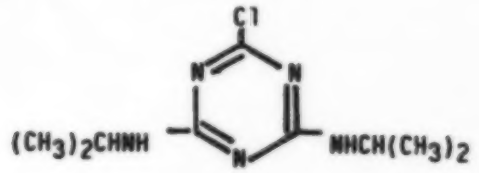
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
DNA	Deoxyribonucleic acid
i.p.	Intraperitoneal
LD_{50}	Dose lethal to 50% of recipients
ppm	Parts per million
RNA	Ribonucleic acid
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Propazine is the common name for 2-chloro-4,6-di(isopropylamino)-1,3,5-triazine. Other chemical synonyms and product names include 2-chloro-4,6-bis(isopropylamino)-s-triazine, 6-chloro-N,N'-bis(1-methylethyl)-1,3,5-triazine-2,4-diamine, Milogard (U.S.A.) and Gesamil (Europe). The structural formula for propazine is as follows:



The molecular formula for propazine is $C_9H_{16}N_5Cl$ and the molecular weight is 229.7. The Chemical Abstracts Service (CAS) Registry number for propazine is 139-40-2.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Propazine is a colorless, crystalline solid. Selected physical and chemical properties are as follows (BCPC, 1977; WSSA, 1979):

Melting point:	212-214°C
Vapor pressure (20°C):	2.9×10^{-9} mm Hg
Solubility:	8.6 mg/l in 20°C water 5.3 mg/l in 20°C water (Calvet et al., 1975) 4.6 mg/l in 26°C water (Ward and Weber, 1968) sparingly soluble in organic solvents
Stability:	stable in neutral, slightly acid or slightly alkaline media
pK_a	1.85 (Weber et al., 1969)
log octanol-water partition coefficient:	2.94 (Brown and Flagg, 1981)

1.3. PRODUCTION DATA

Propazine is synthesized by the reaction of cyanuric chloride with two equivalents of isopropylamine in the presence of an acid acceptor (BCPC, 1977). The technical product is >95% pure.

The sole domestic producer of propazine is the Ciba-Geigy Corporation (Agricultural Division, St. Gabriel, LA) (SRI, 1983). Production quantity data could not be located in the available literature.

1.4. USE DATA

Propazine is widely used for pre-emergence control of broadleaf and grass weeds in selected crops (e.g., sorghum, millet, carrots and other umbelliferae) (BCPC, 1977; WSSA, 1979). Propazine is usually applied as an aqueous spray by ground or aerial equipment.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

Irradiation of propazine in water (0.1 g/ℓ, pH 6.9) with a photochemical lamp (primary UV emission at 253.7 nm) for 24 hours resulted in 2-hydroxypropazine in good yield (Pape and Zabik, 1970). Spectroscopic studies of aqueous propazine (4.2 mg/ℓ) showed maximum absorption at 220 nm, minor absorption at 260 nm, a time-dependent decrease in 260 nm absorbance when photolyzed by photochemical lamp, and a lack of photolysis at wavelengths >300 nm. When a saturated aqueous solution of propazine (pH 4.0) containing a sensitizer (riboflavin) was irradiated with direct sunlight or daylight lamp for 1 hour, 12% N-deisopropylation occurred (Rejto et al., 1983); formation of 2-hydroxypropazine did not occur under these conditions.

Ruzo et al. (1973) determined a zero-order rate constant of 0.28×10^{-10} mole ℓ^{-1} sec^{-1} ($kt=Ao-A$) for the photolysis of propazine (10^{-3} M) in water (pH not stated). The irradiation was performed at 40°C with a light source having a maximum output of 300 nm. The half-life corresponding to this rate constant is calculated to be 2.1 days.

Studies performed with aqueous soil-free systems indicate that chemical hydrolysis of propazine can occur, but that hydrolysis is pH-dependent and very slow between pH 4-6 (Section 2.3.).

2.2. AIR

Specific data regarding the fate or transport of propazine were not located in the available literature. Data summarized in Sections 2.1. and 2.3. suggest that photodegradation and/or chemical hydrolysis could occur, and that propazine could exist sorbed to particulates.

2.3. SOIL

The chloro-s-triazine herbicides are considered to have low to moderate mobility in soil (Helling, 1970), but only limited specific data are available for propazine. Leaching of propazine appears to be limited by its moderately low water solubility (8.6 mg/L) and adsorption to soil constituents (e.g., organic matter, clay). The log K_{oc} for propazine has been reported to be 2.56 (Brown and Flagg, 1981).

Burnside et al. (1969) applied propazine at rates of 3 and 9 lb/A to soils with different textures (sandy loam, very fine sandy loam, silt loam, silty clay loam) and average annual rainfall (15, 22 or 28 inches) from six locations across Nebraska. When soybeans were greenhouse-grown in soil samples from various depths (0-3, 3-6, 6-12, 12-24 and 24-36 inches) taken 4 months following application, the percentage reduction in crop yields indicated that propazine was concentrated in the top 6 inches. In another study that used a plant bioassay to evaluate depth of leaching, propazine was applied at rates of 2 or 4 lb/A to the surface of soil columns that contained Lakeland fine sandy soil and were irrigated with 1 or 2 inches of water at biweekly intervals for up to 4 weeks (Rodgers, 1968). Oat and cucumber seeds were planted in soil samples that were taken 1-23 inches from the top of the column 7 days after the last irrigation, and depth of leaching was considered to be the greatest depth from which a soil sample had plants that died during a growing period of 28 days. The maximum depth of leaching (means of treatment schedules and both crops) was determined to be 8.5 inches, but soil from 23 inches (bottom of column) was lethal to carrots following treatment with 4 lb/A propazine and maximum irrigation (2 inches of water biweekly for 4 weeks).

Popov (19 d in an abstract of a Russian study that a lower concentration o. ne (1.0-1.5 kg/ha) penetrated to 10 cm (~3.9 inches) in an alluvial . (3.1% organic matter) during the growing season. Penetration was 10-20 cm (~3.9-7.8 inches) at a higher concentration (2.0 kg/ha), but 60% was retained in the 0-5 cm (~2 inches) zone.

Other soil column and phytotoxicity studies (Harris, 1967a; Rahman and Matthews, 1979) and a soil thin-layer chromatography study (Helling and Turner, 1968) have shown that propazine mobility decreases, as is expected, with increased clay and/or organic matter content. The adsorption of propazine by soil organic matter in aqueous solutions has been demonstrated to be pH-dependent, decreasing with increasing acidity (Weber et al., 1969; Nearpass, 1972). Since the pK_a of propazine is 1.85, adsorption at typical soil pH will occur largely as unchanged molecules.

The Burnside et al. (1969) study showed that phytotoxic levels of propazine persisted in most of the soils for at least 28 months after treatment. The yields of top growth of field-grown winter wheat were significantly reduced 40 days after planting the year of treatment and 40 days after planting the year following treatment; grain yields were reduced in 4 of 6 soils treated with 9 lb/A (but not when treated with 3 lb/A) the spring following the second-year planting.

Chemical hydroxylation appears to be a major mechanism for degradation of propazine in soil. The degradation of randomly ring-labeled ^{14}C-propazine in soils was investigated by Harris (1967b). Duplicate samples of Lakeland sandy loam (pH 6.2), Hagerstown silty clay loam (pH 5.5) and Wehadkee silt loam (pH 5.6) were treated with 1 ppm propazine and incubated at 30°C for up to 8 weeks. Periodic (every 2 weeks for 8 weeks) methanol extractions recovered decreasing amounts of radioactivity; the average

percent recovery in the four soils after 8 weeks was ~65%. Analyses of methanol and NaOH extracts of the 8-week samples showed that 39, 34 and 45% of the initial propazine was recovered as 2-hydroxypropazine in the Hagerstown, Lakeland and Wehadkee soils, respectively. In a similarly designed follow-up study, addition of 200 ppm sodium azide (a microbial inhibitor) to soil (type not specified) reportedly did not prevent the accumulation of the hydroxy derivative.

Nearpass (1972) determined the rate of aqueous hydrolysis of propazine (20 ppm) over the pH range from 2.4-6.0. Hydrolysis followed first-order kinetics at a particular pH and was found to be pH-dependent, increasing with a decrease in pH. Hydrolysis was very slow above pH 4; after 231 days, 60 and 80% of the original propazine remained at pH 5 and pH 6, respectively. The presence of soil organic matter enhanced hydrolysis regardless of pH and the increased hydrolysis was associated with adsorption of propazine by the organic matter, which has an acidic surface.

Propazine-degrading bacteria (Arthrobacter sp., Microbacterium sp., Pseudomonas sp.) and a fungus (Aspergillus fumigatus Fres) have been isolated from soil (Kaufman and Kearney, 1970), but data regarding the route or extent of degradation were not available. MacRae and Alexander (1965) reported that $^{14}CO_2$ was not detected when ^{14}C-propazine was incubated with Honeoye silt loam for up to 16 weeks at 25°C, but the position of the label was not specified. The significance of biodegradation is difficult to evaluate from the limited available data for propazine, but studies with other chloro-s-triazines suggest that the major mechanism of microbial degradation probably involves dealkylation and/or deamination (although dechlorination/hydroxylation at the number two carbon and ring cleavage may also occur) and that chemical hydroxylation is more rapid in soils than microbial degradation.

Data summarized in Section 2.1. suggest that photodecomposition of propazine can occur near the surface of moist soils, particularly if sensitizer materials are present, but additional data are not available.

3. EXPOSURE

3.1. WATER

Propazine has been detected at levels <0.1 µg/ℓ in the finished drinking water from three New Orleans area water treatment facilities (Keith et al., 1976). In another study, propazine was detected in wastewater (0.5-3.5 mg/ℓ), river water (0.01-0.45 mg/ℓ) and sediment (4.5-12 mg/ℓ) samples from an isolated but unspecified specialty chemicals manufacturing plant, but not in Delaware River water in the vicinity of multiple chemical companies (Jungclaus et al., 1978; Hites et al., 1979).

The mean concentration of propazine in 1003 samples of whole water was reported in STORET to be 0.1 µg/ℓ (range 0-100 µg/ℓ). Detailed printouts of 189 of the stations indicate that this mean reflects detection of high levels of propazine in stream water in several locations and does not imply widespread occurrence of detectable propazine in ambient water; it appears that propazine was not detected in most of the samples.

3.2. FOOD

Propazine is absorbed by plant roots, is translocated, and accumulates in the apical meristems and leaves of plants (WSSA, 1979). Although biotransformation of propazine may occur in crops, i.e., corn (Sheets, 1970), it is possible that residues of unchanged propazine can occur. Specific data on levels of propazine residues in harvested crops were not, however, located in the available literature.

3.3. INHALATION

Pertinent data regarding the levels of propazine in air could not be located in the available literature.

3.4. DERMAL

Pertinent data regarding the levels of propazine on skin could not be located in the available literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

Elimination data indicate that propazine is rapidly absorbed by the gastrointestinal tract of rats as shown in Section 4.4. (Bakke et al., 1967). Elimination of radioactivity from orally administered ring-labeled (urine) or isopropyl-labeled (expired CO_2 and urine) ^{14}C-propazine (41-56 mg/kg) was most rapid during the first 24 hours (~37 and 65% of the administered radioactivity was eliminated, respectively).

Orton et al. (1973) reported that the uptake of ^{14}C-propazine (position of label not specified) by isolated perfused rabbit lungs was <15%. Uptake reflected the disappearance of label from blood that contained 3 µmol of propazine after 60 minutes of perfusion.

4.2. DISTRIBUTION

Radioactivity was fairly evenly distributed throughout body tissues (liver, lung, spleen, kidney and heart) of two rats following single oral doses of uniformly ring-labeled ^{14}C-propazine, but progressively declined so that the levels after 8 days were ~50% of the levels after 2 days (Bakke et al., 1967). Levels of radioactivity in the brain were consistently lower, however, than in the other tissues. Analyses after 12 days showed that ^{14}C activity in the hide and hair was ~6 times higher than the eviscerated carcass, and that carcass levels were comparable to total thoracic and abdominal visceral levels; levels in individual tissues were not determined after 12 days.

4.3. METABOLISM

The metabolic fate of propazine has been incompletely characterized in the rat. The limited available data indicate that N-dealkylation is the predominant route of degradation but that ring cleavage does not occur.

Boehme and Baer (1967) administered unlabeled propazine by gavage to rats weighing 200-300 g in single doses of 50-200 mg/animal and examined the urine for metabolites after 72 hours. 2-Chloro-4,6-diamino-1,3,5-triazine, 2-chloro-4-amino-6-isopropylamino-1,3,5-triazine and 2-chloro-4-amino-6-[1-(1-carboxy)ethyl]amino-1,3,5-triazine were qualitatively identified as metabolites, indicating that N-dealkylation and N-alkyl oxidation to acid occurred. In another study, propazine was similarly administered to rats weighing ~300 g at doses of 0.005, 0.05, 5 or 50 mg/day for 3 days (Bradway and Moseman, 1982). Urine was collected for 24 hours after each dose and for 4 days following the last dose, and analyzed for metabolites. 2-Chloro-4,6-diamino-1,3,5-triazine appeared to be the major metabolite, constituting 3.3 and 0.3% of the administered 5 and 0.5 mg/day doses, respectively, after day 1; 9.6 and 17% of the respective total doses were excreted after 3 days of administration. Rats exposed to 50 or 5 mg/day propazine reportedly excreted 0.5 or 0.1% of the total 3-day dose as 2-chloro-4-amino-6-isopropylamino-1,3,5-triazine and 2-chloro-4-amino-6-ethylamino-1,3,5-triazine; the principal metabolite was expected to be the first compound, but this was not verified analytically.

Bakke et al. (1967) administered uniformly ring-labeled ^{14}C-propazine and bis(isopropyl-2-^{14}C)-labeled propazine to rats by gavage in single doses of 41-56 mg/kg. Ion exchange chromatography of the urine indicated at least 18 metabolites, but identification was not performed. Appearance of 50% of the radioactivity from the isopropyl-labeled propazine in the expired air indicated that at least one of the isopropyl groups was removed from the ring, but cleavage of the ring was not indicated because $^{14}CO_2$ was not detected in the expired air of the ring-labeled propazine-treated rats.

Conjugation of propazine by mouse liver glutathione S-transferases has been demonstrated in an <u>in vitro</u> study (Guddewar and Dauterman, 1979).

Experiments with related 1,3,5-triazines suggested that a chloro group at the 2-position may be required for conjugation.

4.4. ELIMINATION

Bakke et al. (1967) found that the elimination of single oral doses (41-56 mg/kg) of uniformly ring-labeled ^{14}C-propazine (five rats) and ^{14}C-propazine that was labeled at the 2-position of the isopropyl groups (two rats) was rapid. Radioactivity measurements indicated that elimination was most rapid during the first 24 hours, decreasing to trace amounts after 48-72 hours. Most of the ring-labeled ^{14}C-propazine activity was eliminated in the urine (~37% of administered dose in 24 hours, 65.8% in 72 hours), with a lesser amount in the feces (~5% in 24 hours, 23% in 72 hours), but radioactivity was not detected in the respiratory gases. Approximately 45 and 48%, 20 and 21%, and 2 and 13% of the administered isopropyl-labeled ^{14}C-propazine radioactivity was eliminated after 24 and 48 hours in the expired CO_2, urine and feces, respectively. After 72 hours, a total of 89% of the administered dose of isopropyl-labeled ^{14}C-propazine was recovered in the CO_2, urine and feces.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of propazine could not be located in the available literature.

5.2. MUTAGENICITY

Reverse mutation testing of propazine in the spot test with eight unspecified histidine-requiring mutants of Salmonella typhimurium (Ames assay) was negative, but exogenous mammalian metabolic activation was not employed (Andersen et al., 1972). Propazine also did not induce rII mutants in T_4 bacteriophage or induce reversion of bacteriophage AP72 to T_4 phenotype (Andersen et al., 1972).

Propazine was not differentially toxic to wild-type (H17 Rec^+) or DNA repair-deficient (M45 Rec^-) strains of Bacillus subtilis (negative Rec-assay) when tested without metabolic activation (Shirasu, 1975; Shirasu et al., 1976).

It was reported in an abstract of a Russian study (Kulakov, 1970) that i.p. administration of propazine to rats at doses 0.033-0.1 times the LD_{50} depressed mitotic activity, inhibited mitosis in prophase, produced fused chromosomes and produced a slight increase in the incidence of chromosomal fragments in bone marrow cells.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of propazine could not be located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of propazine could not be located in the available literature.

5.5. CHRONIC TOXICITY

The results of two unpublished Ciba-Geigy subchronic toxicity studies are briefly summarized by WSSA (1979). Male and female rats that received propazine (route and formulation not specified) at a dose of 250 mg/kg/day reportedly did not exhibit gross or microscopic evidence of toxicity after 130 consecutive days of treatment. "Clinical or physical toxic symptoms" were not observed in beagle dogs that were fed 50, 200 or 1000 ppm of propazine 80W for 90 days. Additional data regarding the design or results of these studies could not be located in the available literature.

Abstracts of Russian studies indicate that oral administration of propazine to rats at doses of 5-50 mg/kg/day for 2-4 months or 500 mg/kg/day for 10 days to 4 months can elicit the following effects: hypochromic anemia; inhibition of myelopoiesis; increased formation of fetal type Hb; decreased levels of soluble proteins, DNA and RNA in the brain; and decreased DNA and increased RNA content in the liver (Kuznetsova, 1970; Semencheva and Kuznetsova, 1975). It was noted in an abstract of another Russian study (Semencheva et al., 1972) that daily oral administration of 500 mg/kg propazine to rabbits for 1-4 months caused hypochromic macrocytic anemia, antierythrocyte antibodies in the blood serum, increased synthesis of embryonic forms of Hb (HbF and HbII), and decreased levels of soluble protein, DNA and RNA in the bone marrow. Concurrent administration of thymidine reportedly prevented the reduction of DNA and RNA in the rat brain or liver and rabbit bone marrow. Additional information regarding the Russian studies was not reported, but it should be noted that all were conducted by the same group of investigators.

5.6. OTHER RELEVANT INFORMATION

Secondary reference sources report that the acute oral LD_{50} for propazine in rats and mice is >500 mg/kg and that signs of intoxication in laboratory animals include ataxia, dyspnea and convulsions (BCPC, 1977; WSSA, 1979). Oral LD_{50}s of >7500 mg/kg for rats (Dinerman and Lavrent'eva, 1969) and 4670 mg/kg for rabbits (Mazol and Urbanovich, 1976) have been reported in abstracts of Russian studies. The Russian studies also indicated that toxic effects of the acute exposures included decreased blood pyruvic acid level, decreased adrenal weight, decreased liver and adrenal ascorbic acid content and increased urinary excretion of ascorbic acid and 17-keto-steroids in the rats, and gross pathological changes (i.e., altered color and texture) in the liver, kidney and heart in the rabbits.

Mortality or unspecified signs of toxicological or pharmacological responses were not observed in rats that were exposed to a dust aerosol (1.8-4.9 mg/m^3, reportedly the highest concentration obtainable) of propazine 80W for 1 hour (WSSA, 1979).

6. AQUATIC TOXICITY

6.1. ACUTE EFFECTS

Triazines, including propazine, were reportedly toxic to the guppy, Poecilia reticulata, at concentrations of 1-6.5 mg/ℓ (Tscheu-Schleuter, 1976). Toxicity was not defined and additional data were not reported in the abstract of this East German study.

6.2. CHRONIC EFFECTS

It was noted in an abstract of a Romanian study (Marcoci and Ionescu, 1979) that propazine was toxic to all fish studied (Cyprinus carpio, Pseudorazbora parva, Leucaspius delineatus) after 10-14 days. Toxicity was not defined and additional data were not reported.

6.3. PLANT EFFECTS

Propazine has been reported to be a strong photosynthesis poison for the green alga, Ankistrodesmus falcatus (Tscheu-Schlueter, 1976).

6.4. RESIDUE

Pertinent data regarding the residues of propazine could not be located in the available literature.

6.5. OTHER RELEVANT INFORMATION

The effects of pH on the toxicity (median tolerance concentration) of 274 pesticides to fish, Oryzias latipes, Cyprinus carpio and Bufo vulgaris formosus, were studied by Nishiuchi (1980), but the report is not available in English.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Guidelines and standards for occupational or environmental exposure to propazine have not been recommended or promulgated.

7.2. AQUATIC

Guidelines or standards for the protection of aquatic organisms from the toxic effects of propazine could not be located in the available literature.

8. RISK ASSESSMENT

The toxicity of propazine cannot be assessed adequately from the available data. The WSSA (1979) reported that Ciba-Geigy found that doses of 250 mg/kg/day for 130 days (route not specified) did not produce gross or microscopic evidence of toxicity in rats, and that 50, 200 or 1000 ppm propazine in the diet for 90 days did not produce "clinical or physical toxic symptoms" in dogs. Abstracts of Russian studies indicate that subchronic oral administration of propazine to rats (5-50 mg/kg/day for 2-4 months, 500 mg/kg/day for 10 days to 4 months) or rabbits (500 mg/kg/day for 1-4 months) can elicit effects such as hypochromic anemia, increased formation of fetal-type hemoglobin and alterations in the levels of nucleic acids in the brain, liver or bone marrow (Kuznetsova, 1970; Semencheva and Kuznetsova, 1975; Semencheva et al., 1972). It should be emphasized, however, that the Ciba-Geigy studies are unpublished, that summaries of all the studies were published in secondary references; and that additional data regarding the design or results of any of the studies were not availble for review. These factors preclude derivation of an ADI from any of the reported no-effect or effect levels.

Limited data suggest that propazine is not a direct mutagen in bacterial systems (Andersen et al., 1972; Shirasu, 1975; Shirasu et al., 1976), but carcinogenicity, teratogenicity and reproductive effects testing have not been reported in the available literature.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence.

These data, which are considered Confidential Business Information, are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment, however, can be presented in this chapter.

This CBI Appendix to this document reviews in greater detail the unpublished studies in rats and dogs mentioned above; however, other animal studies are also reviewed that indicate that propazine is carcinogenic to rats. A q_1^* for humans of 7.79×10^{-2} $(mg/kg/day)^{-1}$ was calculated from dose-response data for mammary gland tumors in female rats fed propazine in the diet. The q_1^* value was calculated using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). The conversion factor used in the calculation of this q_1^* value for humans (assuming 70 kg body weight) from animal data is the cube root of the body weight ratio (Federal Register, 1980).

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